IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
REQUEST FOR FILING NATIONAL PHASE OF PCT APPLICATION UNDER 35 U.S.C. 371 AND 37 CFR 1.494 OR 1.495

09/831290

To: Hon. Commissioner of Patents
Washington, D.C. 20231

00909

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)

Atty Dkt: P 279455 /Z70429/UST
M# /Client Ref.

From: Pillsbury Winthrop LLP, IP Group:

Date: May 8, 2001

This is a **REQUEST** for **FILING** a PCT/USA National Phase Application based on:

1. International Application: PCT/GB99/03789 (⇧ country code)
2. International Filing Date: 12 (Day) November (MONTH) 1999 (Year)
3. Earliest Priority Date Claimed: 17 (Day) November (MONTH) 1998 (Year) (use item 2 if no earlier priority)
4. Measured from the earliest priority date in item 3, this PCT/USA National Phase Application Request is being filed within:

   (a) ☐ 20 months from above item 3 date (b) ☒ 30 months from above item 3 date,

   (c) Therefore, the due date (unextendable) is May 17, 2001
5. Title of Invention METHOD FOR IDENTIFYING INHIBITORS OF IPC SYNTHASE
6. Inventor(s) SCHNELL, Norbert Friedemann et al

Applicant herewith submits the following under 35 U.S.C. 371 to effect filing:

7. ☒ Please immediately start national examination procedures (35 U.S.C. 371 (f)).
8. ☒ **A copy of the International Application** as filed (35 U.S.C. 371(c)(2)) is transmitted herewith (file if in English but, if in foreign language, file only if not transmitted to PTO by the International Bureau) including:

   a. ☒ Request;
   b. ☒ Abstract;
   c. 7 pgs. Spec. and Claims;
   d. 2 sheet(s) Drawing which are ☐ informal ☒ formal of size ☒ A4 ☐ 11"
9. ☒ **A copy of the International Application has been transmitted by the International Bureau.**
10. **A translation of the International Application** into English (35 U.S.C. 371(c)(2))
    a. ☐ is transmitted herewith including: (1) ☐ Request; (2) ☐ Abstract;
       (3) _____ pgs. Spec. and Claims;
       (4) _____ sheet(s) Drawing which are:
       ☐ informal ☐ formal of size ☐ A4 ☐ 11"
    b. ☐ is not required, as the application was filed in English.
    c. ☐ is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.
    d. ☐ Translation verification attached (not required now).

RE: USA National Phase Filing of PCT /GB99/03789

JC08 Rec'd PCT/PTO 08 MAY 2001

11. ☒ Please see the attached Preliminary Amendment

12. ☐ Amendments to the claims of the International Application **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., before 18th month from first priority date above in item 3, are transmitted herewith (file only if in English) including:**

13. ☒ PCT Article 19 claim amendments (if any) have been transmitted by the International Bureau

14. ☐ Translation of the amendments to the claims **under PCT Article 19 (35 U.S.C. 371(c)(3)), i.e., of claim amendments** made before 18th month, **is attached (required by 20th month from the date in item 3 if box 4(a) above is X'd, or 30th month if box 4(b) is X'd, or else amendments will be considered canceled).**

15. **A declaration of the inventor** (35 U.S.C. 371(c)(4))
a. ☒ is submitted herewith ☒ Original ☐ Facsimile/Copy
b. ☐ is not herewith, but will be filed when required by the forthcoming PTO Missing Requirements Notice per Rule 494(c) if box 4(a) is X'd or Rule 495(c) if box 4(b) is X'd.

16. **An International Search Report (ISR):**
a. Was prepared by ☒ European Patent Office ☐ Japanese Patent Office ☐ Other
b. ☒ has been transmitted by the international Bureau to PTO.
c. ☒ copy herewith (1 pg(s).) ☐ plus Annex of family members (___ pg(s).).

17. **International Preliminary Examination Report** (IPER):
a. ☒ has been transmitted (if this letter is filed after 28 months from date in item 3) in English by the International Bureau with Annexes (if any) in original language.
b. ☒ copy herewith in English.
c.1 ☐ IPER Annex(es) in original language ("Annexes" are amendments made to claims/spec/drawings during Examination) including attached amended:
c.2 ☐ Specification/claim pages #_____ claims #
Dwg Sheets #
d. ☐ Translation of Annex(es) to IPER **(required by 30th month due date, or else annexed amendments will be considered canceled).**

18. **Information Disclosure Statement** including:
a. ☒ Attached Form PTO-1449 listing documents
b. ☐ Attached copies of documents listed on Form PTO-1449
c. ☒ A concise explanation of relevance of ISR references is given in the ISR.

19. ☒ **Assignment** document and Cover Sheet for recording are attached. Please mail the recorded assignment document back to the person whose signature, name and address appear at the end of this letter.

20. ☐ Copy of Power to IA agent.

21. ☐ **Drawings** (complete only if 8d or 10a(4) not completed): ___ sheet(s) per set: ☐ 1 set informal; ☐ Formal of size ☐ A4 ☐ 11"

22. Small Entity Status ☒ is **Not** claimed ☐ is claimed (**pre**-filing confirmation required)
22(a) _____ (No.) Small Entity Statement(s) enclosed (since 9/8/00 Small Entity Statements(s) not essential to make claim)

23. **Priority** is hereby claimed under 35 U.S.C. 119/365 based on the priority claim and the certified copy, both filed in the International Application during the international stage based on the filing in (country) GREAT BRITAIN of:

	Application No.	Filing Date		Application No.	Filing Date
(1)	9825055.8	Nov. 17, 1998	(2)		
(3)			(4)		
(5)			(6)		

a. ☒ See Form PCT/IB/304 sent to US/DO with copy of priority documents. If copy has not been received, please proceed promptly to obtain same from the IB.
b. ☐ Copy of Form PCT/IB/304 attached.

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24. Attached: 3 Pages of Sequence Listing and 1 copy of form PCT/IB/306

25 Per Item 17.c2, **cancel original** pages #_____, claims #_____, Drawing Sheets #

26. **Calculation of the U.S. National Fee (35 U.S.C. 371 (c)(1)) and other fees is as follows:**
Based on amended claim(s) per above item(s) ☐ 12, ☐ 14, ☐ 17, ☐ 25 (hilite)

Total Effective Claims	7	minus 20 =	0	x $18/$9 =	$0	966/967
Independent Claims	3	minus 3 =	0	x $80/$40 =	$0	964/965
If any proper (ignore improper) Multiple Dependent claim is present,				add$270/$135	+0	968/969

BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(4)): →→ **BASIC FEE REQUIRED, NOW** →→→→

A. If country code letters in item 1 are **not** "US","BR","BB","TT","MX","IL" "NZ", "IN" or "ZA"

See item 16 re:

1. Search Report was not prepared by EPO or JPO	add$1000/$500		960/961
2. Search Report was prepared by EPO or JPO	add$860/$430	+860	970/971

SKIP B, C, D AND E UNLESS country code letters in item 1 are "US","BR","BB","TT","MX","IL", "NZ", "IN" or "ZA"

→ ☐ B.	If USPTO did not issue both International Search Report (ISR) and (if box 4(b) above is X'd) the International Examination Report (IPER),	add$1000/$500	+0	960/961
☐ C.	If USPTO issued ISR but not IPER (or box 4(a) above is X'd),	add$710/$355	+0	958/959
→ ☐ D.	If USPTO issued IPER but IPER Sec. V boxes not all 3 YES,	add$690/$345	+0	956/957
→ ☐ E.	If international preliminary examination fee was paid to USPTO and Rules 492(a)(4) and 496(b) satisfied (IPER Sec. V all 3 boxes YES for all claims),	add $100/$50	+0	962/963

27. **SUBTOTAL =** $860

28. If Assignment box 19 above is X'd, add Assignment Recording fee of ----$40 +40 (581)

29. Attached is a check to cover the ---------- **TOTAL FEES** $900

Our Deposit Account No. 03-3975
Our Order No. 9901 (C#) | 279455 (M#)

00909

CHARGE STATEMENT: The Commissioner is hereby authorized to charge any fee specifically authorized hereafter, or any missing or insufficient fee(s) filed, or asserted to be filed, or which should have been filed herewith or concerning any paper filed hereafter, and which may be required under Rules 16-18 and 492 (missing or insufficient fee only) now or hereafter relative to this application and the resulting Official document under Rule 20, or credit any overpayment, to our Account/Order Nos. shown above for which purpose a duplicate copy of this sheet is attached.
This CHARGE STATEMENT does not authorize charge of the issue fee until/unless an issue fee transmittal form is filed

Pillsbury Winthrop LLP
Intellectual Property Group

By Atty: Donald J. Bird **Reg. No.** 25323

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Atty/Sec: DJB/mhn

NOTE: File in duplicate with 2 postcard receipts (PAT-103) & attachments.

09/831290
JC08 Rec'd PCT/PTO 08 MAY 2001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION OF

Inventor(s): SCHNELL, Norbert Friedemann et al

Filed: Herewith

Title: METHOD FOR IDENTIFYING INHIBITORS OF IPC SYNTHASE

May 8, 2001

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE SPECIFICATION:

At the top of the first page, just under the title, insert

☒ --This application is the National Phase of International Application PCT/GB99/03789 filed November 12, 1999 which designated the U.S. and that International Application

☒ was ☐ was not published under PCT Article 21(2) in English.--

Respectfully submitted,

PILLSBURY WINTHROP LLP
Intellectual Property Group

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of

OLIVER et al.

Appln. No.: 09/750,227 Group Art Unit: Unassigned

Filed: December 29, 2000 Examiner: Unassigned

Title: SYSTEM AND METHOD FOR PROVIDING AUTHENTICATION AND VERIFICATION SERVICES IN AN ENHANCED MEDIA GATEWAY

* * * * *

July 3, 2001

PRELIMINARY AMENDMENT

Hon. Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to initial examination on the merits, please amend the above-identified application as follows:

IN THE CLAIMS:

Please enter the following amended claim 15:

15. The system according to claim 11, wherein the first and second users use client devices configured to communicate with each other and with the authentication server.

REMARKS

Consideration and allowance of the present application is respectfully requested. By this Amendment, claim 15 is amended to correct a clerical error and to merely clarify its dependency on independent claim 11.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached Appendix is captioned **"Version with markings to show changes made"**.

In view of the foregoing, the present application is in a condition for allowance and a Notice to that effect is earnestly solicited.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: _____

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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claim 15 as follows:

15. The system according to claim [1] 11, wherein the first and second users use client devices configured to communicate with each other and with the authentication server.

METHOD FOR IDENTIFYING INHIBITORS OF IPC SYNTHASE

The present invention relates to a cell-based screen for inhibitors of fungal inositolphosphoryl-ceramide (IPC) synthase, an important antifungal target.

Inhibitors of fungal IPC synthase are potent and selective antifungal agents for example Aureobasidin, Khafrefungin and Rustmicin) as identified by several research groups and pharmaceutical companies.

However, all such compounds are natural products that are difficult to produce, handle and administer to a patient (for example, they may have unsuitable pharmacokinetics). Therefore it is highly desirable to obtain other novel chemical compounds selectively inhibiting the same target (a fungal IPC synthase) but without the intrinsic disadvantages displayed by the currently known inhibitors. Screening for such novel chemicals as well as optimisation of already available "leads" (ie. optimisation of a known inhibitor in a structure-based design or lead optimisation) will require an assay for IPC synthase activity that can be performed at a sufficiently high throughput.

All currently available biochemical assays for IPC synthase are involved and very labour-intensive.

Nagiec et al (Journal of Biological Chemistry, Vol 272 No 15, pp 9809-9817 (1997))) describe the complementation of an IPC synthase gene defect in a mutant strain of *S. Cerevisiae* by the *AUR1* gene. The mutant strain has a deletion of the LCB1 gene and a point mutation that creates the suppressor gene SLC1-1. The lcb1 mutation prevents sphingolipid synthesis and the SLC-1-1 gene enables the cells to make phospholipids and remain viable. (Use of capital letters implies a functional gene or a gain of function mutation such as SLC1-1 whereas small letters indicate a non functional allele such as lcb1). Using this the authors were able to isolate a mutant strain defective in IPC synthase and to isolate a gene AUR1 which complemented the IPC synthase defect and restored IPC synthase activity. The authors conclude that IPC synthase is the target for antifungal agents such as aureobasidin. They postulate that it should be possible to develop high throughput screens to identify new inhibitors of IPC synthase to combat fungal diseases.

However we have found that whilst a similar strain of *S. cerevisiae* (lcb1 / SLC1-1) is viable, the strain grows very poorly and is extremely sensitive to any environmental

influences such as for example freezing. This strain is simply not robust enough for screening purposes.

We now provide a robust cell-based assay for identifying selective IPC synthase inhibitors. This assay is based on our development of an *S. cerevisiae* strain wherein the production of compensatory phospholipids is enhanced.

Therefore in a first aspect of the present invention we provide a screening assay for identifying a selective IPC synthase inhibitor which assay comprises contacting a test compound with engineered cells whose capability to synthesize sphingolipids depends on the addition of exogenous phytosphingosine and which are capable of sustained growth via compensatory phospholipids, adding phytosphingosine, and determining IPC synthase inhibition by the test compound by reference to any cell growth inhibition.

Any convenient host cell strain may be used provided that it can function as a host for a fungal IPC synthase gene. Convenient hosts include fungi that are manipulatable genetically such as *S. cerevisiae* but also others such as Candida albicans, Candida glabrata, Aspergillus sp. or Schizosaccharomyces pombe. Convenient sources for the AUR1 gene are pathogenic (also phytopathogenic) fungi as outlined above and others such as Ashbya sp., Fusarium sp., Trichoderma sp., Cryptococci, Blastomyces, and Histoplasma.

Whilst we do not wish to be bound by theoretical considerations the compensatory phospholipids are believed to be novel glycerophospholipids that may compensate for one or more functions of sphingolipids essential for vegetative growth (Lester et al, J.Biol.Chem., 1993, 268, 845-856).

In a further aspect of the invention we provide engineered cells whose capability to synthesize sphingolipids depends on the addition of exogenous phytosphingosine and which are capable of sustained growth via compensatory phospholipids

By "sustained growth" we mean no significant decrease of viable cell counts during a growth period (ie. cell-death is negligible compared to cell growth). The strain also has to be capable of one or more of the following: being stored for prolonged periods, for example up to three or six months or longer; storage in liquid medium; or capable of being frozen and revived. The engineered cells of the invention are capable and robust enough for routine use in high throughput assay procedures. In general they will have generation times compatible with growth assays (ie. not more than 4 hours per doubling) and final optical densities reached

of more than 4 OD (at 600 nm and 1 cm path length). These parameters allow complete assessment of a host strain's growth within less than 30 hours.

A convenient host strain for use in the assay methods of the invention is an lcb1 / SLC1-1 strain. More conveniently it will include a selection marker, for example the lcb1 gene may be directly replaced by an amino acid biosynthetic gene (such as LEU2, TRP1 or HIS3) or antibiotic resistance such as Geneticin (G418).

Adapting host cells for sustained growth is for example achieved by enhancing expression of the compensatory mutant SLC1-1 allele. We have surprisingly found that can be achieved by cloning the SLC1-1 gene onto a multi-copy plasmid (pYES2-LEU2d- GPD3-SLC1-1 = pNS149) under control of the glyceraldehyde 3-phosphate dehydrogenase promoter. Use of a multi-copy pGPD-SLC1-1 promoter/gene construct yielded a strain with much improved growth characteristics, improved growth rate, final optical density and resistance to freezing. In summary it provided for the first time a host strain which is robust enough for screening purposes.

The GPD3 is an example of a very strong constitutive promoter in S. cerevisiae. Other glycolytic enzymes such as Phosphoglycerate Kinase (PGK), Enolase 1 (ENO), Pyruvate Kinase (PYK) and Fructose-Bisphosphate Aldolase II FBA are convenient sources of other such promoters.

Therefore in a further aspect of the invention we provide an engineered host strain *S. cerevisiae* (lcb1 / pGPD-SLC1-1).

The invention will now be illustrated but not limited by reference to the following Examples and Figures:

Examples

Example 1 Construction of the IPC synthase screening strain (lcb1::kanMX, pNS149 (pGPD3-SLC1-1))

(i) Generation of a *LCB1* deletion strain

As *LCB1* is an essential gene, only one allele of a diploid cell can be deleted without loss of survival. Added phytosphingosine can, however, substitute for an intact *LCB1* gene. Technically, one *LCB1* allele of a diploid *S. cerevisiae* strain (JK9-3daa - Kunz, J. et al, Cell, 1993, 73, 585-596) was disrupted using the kanamycin resistance cassette as described by Wach et al, Yeast, 1996, 12, 259-265.

PCR primers used to create the *LCB1* deletion (lcb1::kanMX)

5' Primer :

GCAATGGCACACATCCCAGAGGTTTTACCCAAATCAATACCGATTCCGGCATTTA TTGCAGCTGAAGCTTCGTACGCTGCAG

3' Primer:

CTATTTTTATTTATTAGATTCTTGGCAACAGGCAAGGATGGACTGCTTGACCCGCA TAGGCCACTAGTGGATCTG

Disruption of *LCB1* and its replacement by kanMX was verified by PCR (using primers 5' of the deleted region directed towards the gene and within kanMX facing towards the promoter). Sporulation of the heterozygous diploid (LCB1/lcb1::KanMX) and tetrad dissection yields 2 kanamycin-sensitive colonies per tetrad when grown on YPD (Sherman et al, Methods in Yeast Genetics, 1986, Cold Spring Harbor Laboratory Press, Cold Spring Harbor N.Y. media) without phytosphingosine, however if the ascus is dissected on media containing 10mM phytosphingosine this results in 4 colonies per tetrad, two of which are resistant to kanamycin (and therefore are lcb1::kanMX).

(ii) Generation of a SLC1-1 allele cloned into a multi-copy plasmid

The dominant *SLC1-1* allele was generated from the wildtype allele by PCR regenerating the sequence as described by Nagiec *et al.* (*op cit*). The mutant *SLC1-1* allele differs from the wildtype allele by a single nucleotide which changes Glutamine 44 in the wild-type protein to Leucine in the suppressor protein. According to the literature (Nagiec *et al*, *op cit*) this mutation should rescue the lcb1::kanMX strain, allowing growth on media without added phytosphingosine.

The *SLC1-1* was amplified from genomic DNA by PCR (creating the point mutation via a mismatch in the 5' primer) and cloned into expression plasmids (eg pYES2-Leu2 (Invitrogen), modified by an inserted Leu2 selection marker = pNS144) using BamHI (5') and SphI (3') as insertion sites (to give pNS145). After transformation (5) into lcb1::kanMX (3), (selection SGal-leucine, no phyto-sphingosine added) microcolonies were established after 12 days of incubation proving and confirming the suppressing function of SLC1-1. However, the viability of these transformants was extremely poor and they were not maintainable in liquid culture. Establishment of frozen stocks from the colonies also failed. A similar phenotype was also observed if the homologous SLC1 promoter was used instead of Gal1 (pNS148).

Primers to generate SLC1-1 by PCR. Restriction sites are shown in bold. The point mutation generating Leu 44 is shown underlined in italics

SLC1-1 5'

CGCGGATCCATGAGTGTGATAGGTAGGTTCTTGTATTACTTGAGGTCCGTGTTGGT
CGTACTGGCGCTTGCAGGCTGTGGCTTTTACGGTGTAATCGCCTCTATCCTGTGCA
CGTTAATCGGTAAGCAACATTTGGCTC*T*GTGG

SLC1-1 3'

ACATGCATGCTTAATGCATCTTTTTTACAGATGAACC

(iii) Generation of a GPD3-driven SLC1-1 allele

We postulated that the poor viability of the lcb1::kanMX pNS145 strain might be due to insufficient expression of *SLC1-1*, so increased expression was attempted. We placed the *SLC1-1* gene under control of the glyceraldehyde-3-phosphate dehydrogenase GPD3 (=TDH3), promoter (Norbeck et al, Yeast, 1997, 16, 1519-1534).

The GPD3 promoter was amplified from *S. cerevisiae* chromosomal DNA by PCR and inserted into a HinDIII site of PNS145 (just 5' of the SLC1-1 start ATG) to create plasmid pNS149 which is a further independent aspect of the invention.

PCR primers generating the GPD3 promoter. Restriction sites are shown in bold

PGPD5'
CCC**AAGCTT**GCCGGCACTAGTTCGAGTTTATCATTATCAATACTCGCC

pGPD 3'
GT**AAGCTT**TATTCGAAACTAAGTTCTTGGTG

Transformation (Ito *et al*, J. Bacteriology, 1983, 153, 163-168) of pNS149 into lcb1::kanMX (see 2. above) yielded readily viable colonies, that also grew very well in liquid culture and were able to recover from freeze-storage.

Example 2 The IPC synthase screen

The utility of the lcb1::kanMX pNS149 strain to identify inhibitors of IPC synthase was evaluated using aureobasidinA as a test compound. The lcb1::kanMX pNS149 strain is a further independent aspect of the invention. As shown in Figure 1, the test compound could be readily identified, as predicted. Inhibition by aureobasidinA was very pronounced in the presence of phytosphingosine but absent if no phytosphingosine was added.

Figure 1a

Inhibition of growth by aureobasidinA in strain lcb1::kanMX, pNS149 with added phytosphingosine.

Figure 1b

Inhibition of growth by aureobasidinA in strain lcb1::kanMX, pNS149 without added phytosphingosine.

Claims:

1. A screening assay for identifying a selective IPC synthase inhibitor which assay comprises contacting a test compound with engineered cells whose capability to synthesize sphingolipids depends on the addition of exogenous phytosphingosine and which are capable of sustained growth via compensatory phospholipids, adding phytosphingosine, and determining IPC synthase inhibition by the test compound by reference to any cell growth inhibition.

2. Engineered cells whose capability to synthesize sphingolipids depends on the addition of exogenous phytosphingosine and which are capable of sustained growth via compensatory phospholipids.

3. Cells as claimed in claim 2 wherein the host strain is an lcb1/SLC1-1 strain.

4. Cells as claimed in claim 3 wherein the SLC-1 gene is under the control of the glyceraldehyde 3-phosphate dehydrogenase (GDP3) gene.

5. Cells as claimed in claim 2 wherein the host strain is lcb1/pGPD-SLC-1.

6. S. cerevisiae (lcb1/pGPD-SLC-1).

7. A selective IPC synthase inhibitor identified using the method of claim 1.

Figure 1a

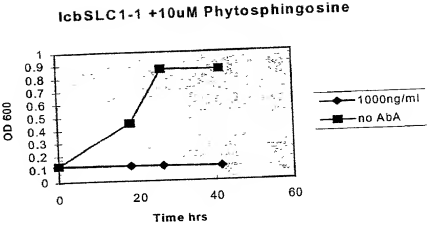
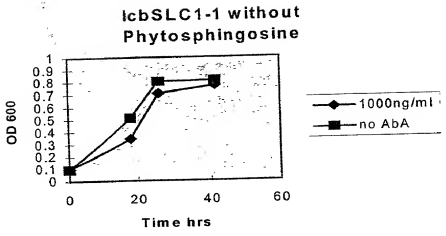

IcbSLC1-1 +10uM Phytosphingosine
OD 600
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
Time hrs
1000ng/ml
no AbA

Figure 1b


IcbSLC1-1 without Phytosphingosine
OD 600
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
Time hrs
1000ng/ml
no AbA

FOR UTILITY/DESIGN
CIP/IPCT NATIONAL/PLANT
ORIGINAL/SUBSTITUTE/SUPPLEMENTAL
DECLARATIONS

RULE 63 (37 C.F.R. 1.63)
DECLARATION AND POWER OF ATTORNEY
FOR PATENT APPLICATION
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PW
FORM
Z7042G/UST

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the **INVENTION ENTITLED METHODS FOR IDENTIFYING INHIBITORS OF IPC SYNTHASE**

the specification of which (CHECK applicable BOX(ES))

X A. ☐ is attached hereto.

BOX(ES) → B. ☐ was filed on _____ as U.S. Application No _____

→ → C. ☐ was filed as PCT International Application No. PCT/GB99 /03789 on 12.11.1999

and (if applicable to U.S. or PCT application) was amended on _____ I hereby state that I have reviewed and understand the contents of the above identified specification including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. Except as noted below, I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for patent or inventor's certificate, or 365(a) of any PCT International Application which designated at least one other country than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International Application, filed by me or my assignee disclosing the subject matter claimed in this application and having a filing date (1) before that of the application on which priority is claimed or (2) if no priority claimed, before the filing date of this application.

PRIOR FOREIGN APPLICATION(S) Number	Country	Day/MONTH/Year Filed	Date first laid-open or Published	Date Patented or Granted	Priority NOT Claimed
9825055.8	GB	17 11 1998			

Except as noted below, I hereby claim domestic priority benefit under 35 U.S.C. 119(e) or 120 and/or 365(c) of the indicated United States applications listed below and PCT international applications listed above or below and, if this is a continuation-in-part (CIP) application, insofar as the subject matter disclosed and claimed in this application is in addition to that disclosed in such prior applications, I acknowledge the duty to disclose all information known to me to be material to patentability as defined in 37 C.F.R. 1.56 which became available between the filing date of each such prior application and the national or PCT international filing date of this application.

PRIOR U.S. PROVISIONAL, NON PROVISIONAL AND/OR PCT APPLICATION(S) Application No. (series code/serial no.)	Day/MONTH/Year Filed	Status Pending, abandoned, patented	Priority NOT Claimed

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 16 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

And I hereby appoint Pillsbury Winthrop LLP, Intellectual Property Group, telephone number (202)861-3000 (to whom all communications are to be directed), and persons of that firm who are associated with USPTO Customer No.909 (see below label) individually and collectively my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent, and I hereby authorize them to delete from that Customer No names of persons no longer with their firm, to add new persons of their Firm to that Customer No., and to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct the above Firm and/or an attorney of that Firm in writing to the contrary

00909

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☐ OR ADDITIONAL INVENTORS see attached page.

☐See additional foreign priorities on attached page (incorporated herein by reference).

Atty. Dkt. No. P_____
(M#)

SEQUENCE LISTING

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<140> GB 9825055.8
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